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ORIGINAL ARTICLE

Once weekly fluconazole for antifungal prophylaxis post-liver transplantation

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Abstract

Background: Invasive fungal infections (IFI) remain a significant cause of morbidity and mortality in orthotopic liver transplantation (OLT) recipients. In this retrospective study, the outcomes of a protocol using once weekly fluconazole for 3 months after OLT in low- and high-risk patients were reviewed.

Methods: In total, 221 OLTs were evaluated in the 3-year period after institution of the new protocol to determine the incidence of IFI within 6 months post-OLT.

Results: In this cohort, 11 IFIs developed during the 6-month post-transplant period, with the majority being non-*albicans Candida*. High-risk patients had a greater rate of IFI (16.7% versus 3.4%, $P = 0.038$) and a significantly longer intensive unit care (ICU) and hospital lengths of stay compared with low-risk patients. Patient and graft survival were similar between the groups. Our patient population appeared to be at low risk for IFI, with 92% of the entire cohort considered low risk.

Discussion: Given the low incidence of IFI in the low-risk group and the possibility of such protocol selecting out for fluconazole-resistant fungi, the use of weekly fluconazole for 3 months may not be justifiable in low-risk OLT recipients. Given the increased resource utilization observed with IFI, further examination of a more intensive prophylactic strategy in high-risk patients may be warranted.

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Introduction

The incidence of invasive fungal infections (IFI) after orthotopic liver transplant (OLT) varies in the literature from 15% to 67%.[1–4] *Candida* and *Aspergillus* are the most common pathogens and these infections predominantly occur within the first 2 months after transplantation.[1] Although IFIs comprise only 20–30% of all infections post-OLT, they are associated with mortality rates of 65–90% for invasive aspergillosis and 30–50% for invasive candidiasis.[1,5] In spite of the high associated morbidity and mortality of such infections post-OLT, the optimal antifungal prophylaxis regimen remains unclear. As a result there is not a consistent centre-to-centre approach. Some centres do not routinely administer antifungal prophylaxis to all liver transplant recipients as a result of the uncertain clinical benefits of prophylaxis, cost, potential toxicity and the risk of emergence of resistance.[5] Other centres have adopted a targeted approach, in which antifungal prophylaxis is provided only to those patients who are at a high risk for IFI. According to a recent survey of North American adult liver transplant centres, 28% practice universal prophylaxis whereas the remaining 72% take a targeted approach to antifungal prophylaxis.[5]

For centres practicing targeted prophylaxis, there is variability regarding the criteria used to define patients who are at high risk for IFI. Furthermore, there is not agreement on the optimal prophylaxis regimen. The preferred agents for targeted prophylaxis among 67 North American adult liver transplant centres include fluconazole in 66%, echinocandins in 21%, amphotericin B in 11% and itraconazole in 2%.[5] There are multiple known risk factors associated with the development of IFI after liver transplantation, with the most common described in Table 1.[2,6–10] The 2009 Infectious Diseases Society of America (IDSA) invasive

Table 1 Risk factors for the development of invasive fungal infections post-orthotopic liver transplant[2,6–10]

Retransplantation
Biliary-enteric anastomosis
Use of > 40 units of cellular blood products (packed red blood cells or platelets intra-operatively)
Pre-transplant renal insufficiency (serum creatinine >2 mg/dl or dialysis)
Operative time >11 h
Fulminant hepatic failure
Peri-operative fungal colonization
Return to operating room within 5 days for intra-abdominal bleeding
Biliary anastomotic leak
Vascular thrombosis
Post-transplant bacterial infection
Post-transplant CMV infection

candidiasis guidelines utilize many of these defined risk factors to classify a patient at high risk for the development of an IFI after liver transplantation.[11]

In August 2005, a protocol was implemented at our facility in which all OLT patients received antifungal prophylaxis with fluconazole 200 mg i.v./p.o. once weekly for 3 months, regardless of the risk factors for IFI. This protocol was used in place of the nystatin swish and swallow suspension given four times daily, each for the prevention of oral candidiasis. The purpose of this protocol change was to offer an agent effective for the prevention of oral candidiasis that was free from drug interactions and significant toxicity, while also providing a less frequent dosing regimen at a lower cost. Given the novelty of this fungal prophylaxis approach, we reviewed the results of this regimen in a large cohort of liver transplant recipients. The purpose of this study was to determine the incidence of IFI in our cohort of patients and to determine if the incidence varied significantly between low- and high-risk recipients. Furthermore, we sought to determine if a once weekly fluconazole approach for the prevention of oral thrush was leading to a higher incidence of fluconazole-resistant fungi.

Methods

Study population

After approval from the Human Research Protection Office at Washington University School of Medicine in St. Louis, we reviewed 255 consecutive OLTs performed between 3 July 2005 and 3 July 2008 at our transplant centre. Clinical and demographic patient data were obtained through both inpatient and outpatient medical records. The Organ Transplant Tracking Record database was primarily used to obtain donor cytomegalovirus (CMV) status, maintenance immunosuppression regimens, and pre- and post-transplant antibiotics or infections unavailable through our inpatient records. All data were analysed per transplant rather than per patient (with the exception of age, gender, race and an age-modified Charlson Comorbidity Index score). For analysis of the outcome measures, the patients were divided into high- and low-risk cohorts based on their risk factors for invasive fungal infections.

Inclusion criteria were age ≥18 years old, OLT procedure during the study period and initiation of fluconazole 200 mg i.v./p.o. weekly immediately post-transplant. Exclusion criteria were death prior to the initiation of fungal prophylaxis or the use of an antifungal regimen other than fluconazole 200 mg i.v./p.o. weekly.

Definitions

High-risk OLT was defined according to the 2009 IDSA candidiasis guidelines as having ≥2 of the risk factors for IFI: re-transplantation, renal insufficiency defined as serum creatinine >2 mg/dL or dialysis within 48 h prior to transplant, biliary-enteric anastomosis, intra-operative use of > 40 units of cellular blood products (packed red blood cells or platelets), operative time >11 h and fungal colonization detected between 2 days before to 3 days after transplant.[11]

Low-risk OLT was any transplant that did not meet the above criteria for high-risk OLT.

Bacterial infection was classified as such if there was a positive culture or documentation of infection in outpatient notes. Blood cultures positive for likely contaminants unless the same organism was isolated from ≥2 blood specimens taken from different sites simultaneously or at different times, but within 7 days of the initial collection were excluded.

CMV viremia was denoted as a positive result on CMV polymerase chain reaction from a blood specimen.

CMV infection was based on evidence of isolation of CMV from urine or throat washings.

CMV disease was defined as clinical evidence of organ dysfunction in addition to isolation or histological evidence of CMV from the affected organ.

Fungal colonization was considered to be isolation of fungus from a non-sterile site (i.e. Jackson–Pratt drain, mucosal surfaces, stool, sputum, urine or wound).

Invasive fungal infection was defined as fungemia, positive cryptococcal or histoplasma antigen, fungus isolated from a normally sterile site (i.e. cerebrospinal fluid, pleural fluid or peritoneal fluid), or positive pathology for fungal elements on biopsy.

Age-modified Charlson Comorbidity Index score predicts 1-year mortality in patients with varying comorbid conditions. The score is derived on a point system in which each comorbid condition is assigned 1, 2, 3 or 6 points depending on the associated risk of mortality with a given comorbidity. The sum of the points predicts the corresponding annual mortality rate: low score (<3), 0.03; moderate score (4–5), 0.13; high score (6–7), 0.27; and a very high score (>8), 0.49.

Outcome measures

The primary endpoint was the development of an IFI within the first 6 months after OLT. Secondary outcomes included graft loss;

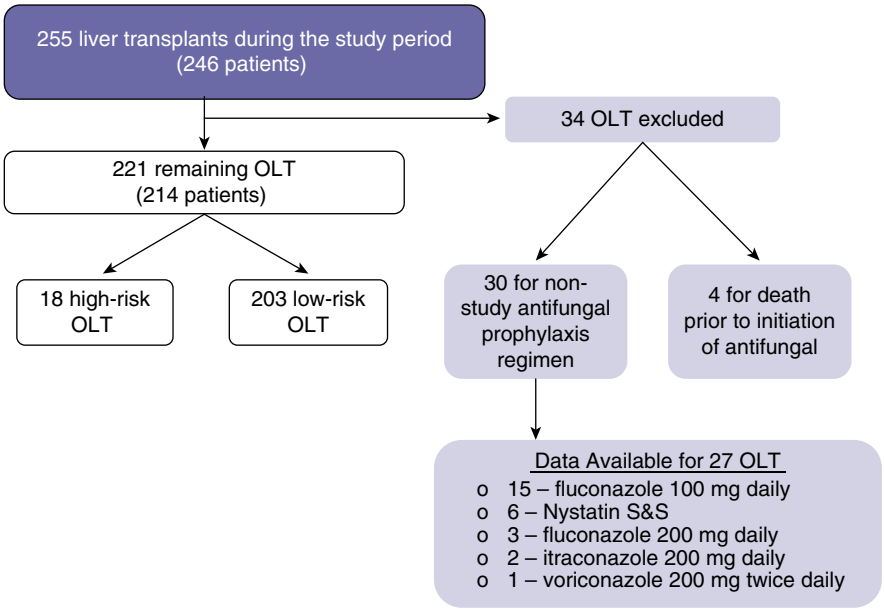

Figure 1 Patient and transplant flow throughout the study

intensive care unit (ICU) and hospital length of stay (LOS); 30-, 60-day, 6- and 12-month mortality.

Statistical analysis

All nominal data were analysed with either the chi-square or Fisher's exact test. The Student's *t*-test was used for parametric continuous data whereas the Mann–Whitney *U*-test was utilized for non-parametric continuous data. Continuous data across more than two groups were analysed using ANOVA. We considered *P*-values less than 0.05 (two-sided) to be statistically significant. We conducted a multivariable analysis using backward logistic regression. All statistical analyses were performed using SPSS, version 16.0 (SPSS Inc., Chicago, IL, USA).

Table 2 Baseline demographics for the 214 unique patients

Characteristic	HR OLT Patients (N = 12)	LR OLT Patients (N = 202)	*P*-value
Age, years (mean ± SD)	51.8 ± 11.8	53.5 ± 9.1	0.13
Male, *n* (%)	8 (66.7%)	133 (65.8%)	1.0
Race, *n* (%)			0.349
Caucasian	12 (100%)	158 (78.2%)	
African American	0	27 (13.4%)	
Other	0	17 (8.4%)	
Age-modified Charlson Comorbidity Index score, median (range)	5.5 (0–9)	5.0 (0–14)	0.796

HR, high risk; OLT, orthotopic liver transplant; LR, low risk.

Results

Patient and transplant characteristics

There were 255 OLTs performed in 246 patients during the study period. Seven patients underwent two OLTs and one patient received three. Thirty-four OLTs were excluded as a result of initiation of an antifungal prophylactic regimen other than fluconazole 200 mg i.v./p.o. weekly (n = 30) or death prior to starting antifungal prophylaxis (n = 4). The remaining 221 OLTs (214 patients) met inclusion criteria. Eight patients underwent simultaneous kidney transplantations, and all met the low-risk criterion. In total, 18 transplants were considered high risk and 203 were considered low risk. Figure 1 summarizes the inclusion and exclusion criteria for this analysis. Baseline characteristics for the 214 patients are summarized in Table 2. When patient demographics were analysed, there were no significant differences between the high- and low-risk cohorts.

Table 3 summarizes the characteristics by transplant. Compared with the low-risk cohort, the high-risk cohort had a significantly higher model for end-stage liver disease score (25 versus 18, $P < 0.001$), requirement for haemodialysis within 48 h prior to transplant (11.1% versus 1%, $P = 0.034$) and were more frequently retransplantations (77.8% versus 1%, $P < 0.001$). The most common indication for OLT in the low-risk group was end-stage liver disease secondary to Hepatitis C cirrhosis (34.5%) and graft failure (55.6%) in the high-risk group. There were significantly more patients in the high-risk group that had graft failure and graft thrombosis as primary indications for OLT, whereas biliary reasons for transplant were significantly more common in the low-risk group, compared with the high-risk group. No difference was found between the two groups regarding the use of antibiotics for ≥72 h, bacterial infection or CMV viremia within the month

Table 3 Characteristics for the 221 OLTs included in the analysis

Characteristic	HR OLT (N = 18)	LR OLT (N = 203)	*P*-value
Admission BMI, mean ± SD	26.9 ± 6	28.7 ± 5.3	0.191
Pre-transplant LOS, days (median, range)	1 (0–28)	0 (0–29)	0.054
Pre-transplant serum creatinine, mg/dl (median, range)	1.5 (1.0–5.3)	1.0 (1.0–8.9)	0.214
Dialysis ≤48 h pre-operative[a]	2 (11.1%)	2 (1.0%)	0.034
Mean calculated Model for End-Stage Liver Disease score	25.4 ± 6.7	18.3 ± 6.3	<0.001
Retransplantation[a]	14 (77.8%)	2 (1.0%)	<0.001
Primary Indication for transplant[a]			
Fulminant hepatic failure	0	5 (2.5%)	1.0
Hepatitis C cirrhosis	2 (11.1%)	70 (34.5%)	0.063
Hepatitis B cirrhosis	0	15 (7.4%)	0.618
Alcoholic cirrhosis	1 (5.6%)	7 (3.4%)	0.499
NASH	0	11 (5.4%)	0.606
Cryptogenic cirrhosis	2 (11.1%)	28 (13.8%)	1.0
Drug-induced hepatotoxicity	0	3 (1.5%)	1.0
Biliary	0	41 (20.2%)	0.029
Polycystic liver disease	0	3 (1.5%)	1.0
Autoimmune hepatitis	0	8 (3.9%)	1.0
Graft thrombosis	3 (16.7%)	2 (1%)	0.004
Graft failure	10 (55.6%)	3 (1.5%)	<0.001
Other[b]	0	7 (3.4%)	1.0
Broad-spectrum antibiotics ≥72 h[ac]	5 (27.8%)	29 (14.3%)	0.165
Bacterial infection[ac]	1 (5.6%)	16 (7.9%)	1.0
CMV donor +/recipient –[a]	3 (16.7%)	13 (16.3%)	0.488
CMV viremia[ac]	0	1 (0.5%)	1.0
Peri-operative fungal colonization[a]	1 (5.6%)	4 (2%)	0.349

[a]Reported as *n* (%).
[b]Other indications include: granulomatous hepatitis, Budd–Chiari syndrome, Wilson's disease, sickle cell disease, amyloidosis, haemorrhagic telangiectasia, and gastric antral vascular ectasia.
[c]Occurred within the 1-month period prior to transplant.
OLT, orthotopic liver transplant; HR, high risk; LR, low risk; BMI, body mass index; LOS, length of stay; NASH, nonalcoholic steatohepatitis; CMV, cytomegalovirus.

prior to transplant. Documented infections in the donors and fungal colonization of the recipients did not differ significantly between the low- and high-risk groups.

Table 4 summarized the intra- and post-operative characteristics of the high- and low-risk transplants. There was no difference in the operating time between the two groups. Transplants in the high-risk groups were significantly more likely to include a biliary-enteric anastamosis (94.4% versus 13.8%, $P < 0.001$) and received significantly more cellular blood products intra-operatively (9.5 versus 5 units, $P = 0.01$) than transplants in the low-risk group. Post-operatively, the rate of total parenteral nutrition (TPN) usage did not differ between the groups; however, the high-risk cohort had a significantly longer median duration of TPN use compared with the low-risk group (median 27.5 versus 6 days, $P = 0.034$). There was no significant difference in the rates of re-operation for bleeding, anastomotic leak or vascular complications between the low- and high-risk groups. The incidence of biopsy-proven acute rejection within 12 months post-transplant did not differ between the two groups.

Immunosuppression, infection prophylaxis and non-fungal infections

Ninety percent of patients in both groups received a tacrolimus–mycophenolate-based immunosuppression regimen. Only those patients who underwent a combined kidney–liver transplant received induction immunosuppression with either thymoglobulin or basiliximab. All patients received methylprednisolone (1 g i.v.) during the anhepatic phase. Post-operatively, steroids were tapered to maintenance (20 mg) prednisone within 5 days. All patients were weaned completely off steroid therapy within 6 months except patients also receiving a kidney transplant who were weaned to 5 mg daily.

No significant difference was found between the groups with regard to infection prophylaxis. Ninety-seven per cent of the

Table 4 Intra-operative and post-transplant characteristics for the 221 OLTs included in the analysis

Characteristic	HR OLT (N = 18)	LR OLT (N = 203)	*P*-value
Intra-operative			
Operative time, hours (mean ± SD)	6.7 ± 2.2	6.5 ± 1.5	0.594
Biliary-enteric anastomosis[a]	17 (94.4%)	28 (13.8%)	1.0
Intra-operative transfusion[a]	15 (83.3%)	151 (74.4%)	0.572
Cellular blood products, units (median, range)	9.5 (1–34)	5 (0–42)	0.01
Post-Transplant			
Re-operation ≤5 days post- transplant[ab]	3 (16.7%)	21 (10.3%)	0.423
TPN required > 24 h[a]	3 (16.7%)	10 (4.9%)	0.077
TPN duration, days (median, range)	27.5 (18–37)	6 (2–51)	0.034
Dialysis ≤72 h post-transplant[a]	1 (11.1%)	5 (2.5%)	0.403
Broad-spectrum antibiotics ≥72 h[a]	10 (55.6%)	80 (39.4%)	0.214
Bacterial infection[ac]	10 (55.6%)	55 (27.1%)	0.016
CMV viremia[ac]	1 (5.6%)	24 (11.8%)	0.701
CMV infection[ac]	0	1 (0.5%)	1.0
CMV disease[ac]	0	2 (1%)	1.0
1-year Biopsy-proven acute rejection[a]	2 (11.1%)	36 (20.2%)	0.745

[a]Reported as n (%).
[b]Re-operation for bleeding, anastomotic leak or vascular insufficiency.
[c]Occurred within the 6-month period after transplant.
OLT, orthotopic liver transplant; HR, high risk; LR, low risk; TPN, total parenteral nutrition; CMV, cytomegalovirus.

patients received trimethoprim–sulfamethoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis. Prophylaxis for CMV infection with valganciclovir was provided in 49 patients (24%) in the low-risk group and 7 patients (39%) in the high-risk group ($P = 0.169$). All other patients received acyclovir as antiviral prophylaxis.

The number of infectious episodes requiring the use of broad-spectrum antibiotics for ≥72 h during the first 6 months post-OLT was not different between the groups; however, the incidence of bacterial infection within 6 months after transplant was significantly greater in the high-risk group (Table 4). The incidence of CMV viremia, CMV infection and CMV disease was not significantly different between the high- and low-risk transplants.

Invasive fungal infections

There were 11 IFIs in 10 OLTs which occurred within the initial 6 months after OLT (Table 5). Three IFIs occurred after high-risk transplants and seven occurred after low-risk transplants. After one low-risk transplant, the patient developed two IFIs by definition; however, these infections were caused by the same organism, occurring at different sites within 1 week of each other. Transplants in the high-risk group were significantly more likely to develop an IFI compared with the low-risk group (16.7% versus 3.4%, $P = 0.038$). The majority of the IFIs were caused by *Candida* species, predominantly non-albicans, and most occurred within the first 1–2 months post-transplant. Susceptibilities were not routinely obtained, with only two IFIs having susceptibility information. Two of the *Candida glabrata* infections (IFI nos 5 and 6 in Table 5) exhibited a dose-dependent susceptibility to fluconazole, which is common for most *C. glabrata* infections.

Table 5 Invasive fungal infection by risk, date of isolation, organism and source

IFI #	Risk of IFI	Date of Isolation	Organism	Source
1	High	POD 22	*C. krusei*	Peritoneal fluid
2	High	POD 43	*C. glabrata*	Peritoneal fluid
3	High	POD 23	*C. parapsilosis*	Blood
4	Low	POD 11	*C. glabrata* *Zygosaccharomyces bailii*	Peritoneal fluid
5	Low	POD 37	*C. glabrata*	Peritoneal fluid
6	Low	POD 43	*C. glabrata*	Blood
7	Low	POD 10, 14, 17	*Cryptococcus neoformans*	Blood
8	Low	POD 26	*C. albicans*	Peritoneal fluid
9	Low	POD 168	*Histoplasma capsulatum*	Blood
10	Low	POD 146	*Candida* pseudohyphae	Esophageal biopsy
11	Low	POD 103	*Scedosporium apiospermum*	Auditory canal biopsy

IFI, invasive fungal infection; POD, post-operative day.

Table 6 summarizes the results for the secondary outcomes. There was no significant difference in graft or patient survival between the high- and low-risk groups. Post-transplant ICU

Table 6 Incidence of graft loss and death for the 221 OLTs included in the analysis

	HR OLT (N = 18)	LR OLT (N = 203)	*P*-value
Graft loss	4 (22.2)	23 (11.3)	0.248
Graft loss as a result of death	4 (22.2)	15 (7.4)	0.055
Graft loss as a result of loss of function	0	8 (3.9)	1.0
Mortality	4 (22.2)	15 (7.4)	0.055
30-day mortality	1 (5.6)	6 (3.0)	0.453
60-day mortality	1 (5.6)	0	0.081
6-month mortality	1 (5.6)	5 (2.5)	0.403
12-month mortality	1 (5.9)	4 (2.3)	0.349

OLT, orthotopic liver transplant; HR, high risk; LR, low risk.

length of stay (LOS) was significantly longer in the high-risk group compared with the low-risk group with a median of 2.7 days (range 1–33) versus 1.8 (range 1–32) ($P = 0.029$). This was also true for overall median hospital LOS of 14.9 (6–68) days versus 7.8 (3–114) days ($P = 0.002$), respectively.

The multivariable analysis of all evaluated OLTs included the following variables: Hepatitis C, alcohol or biliary cirrhosis as a reason for transplant; retransplantation; biliary-enteric anastomosis; re-operation within 5 days; re-operation for biliary anastomotic leak; operation time; TPN duration; ICU LOS; postoperative antibiotics ≥72 h; bacterial infection during the first 6 months after transplant; and low-risk grouping. This analysis indicated that classification as low risk was the only independent variable that was significantly associated with a reduction in the development of IFI (odds ratio = 0.014; 95% confidence interval 0.0001–0.705).

Discussion

Invasive fungal infections continue to be a major concern after liver transplantation. Established IFIs not only carry significant morbidity and mortality in immunosuppressed patients, there is a considerable economic burden associated with IFIs.[1,5,12–14] One recent study conducted in transplant recipients demonstrated that patients that developed an IFI post-transplant resulted in $55 400 in excess costs compared with patients without an IFI.[14] There are defined risk factors for the development of an IFI after OLT which have been validated prospectively.[6] Using these criteria, we demonstrated greater than a four-fold increased risk of IFI within the first 6 months after transplant in patients classified as being at high risk for IFI. While there was no observed increased allograft loss or mortality in our high risk group, it is difficult to draw a conclusion relating to mortality owing to the small high risk cohort size. However, there was a significant increase in resource utilization in these patients as indicated by the longer ICU and hospital LOS. The risks for IFI development are similar to other known risk factors for increased LOS and thus it is difficult to determine what exact role the IFIs played in resource utilization. However, developing an antifungal prophylaxis regimen that is both clinically and cost-effective for all liver transplant recipients is an important component of quality and outcome improvement.

Our patient population appears to be at low risk for IFI overall, as 92% of our study population was considered low risk. For this group of patients, this study shows that fluconazole 200 mg i.v./p.o. weekly results in an IFI rate of 3.4%. This rate of IFI is similar to the 4% rate in a recent report of non-systemic antifungal prophylaxis with nystatin 500 000 units 4 times daily for 60 days.[6] While the use of once-weekly fluconazole provides a benefit of reduced expense, less toxicity than daily fluconazole, no clinically significant drug interactions and a potential for increased compliance and patient satisfaction over the four times daily dosing of non-absorbable agents, the possibility of this regimen selecting out for non-albicans *Candida* and non-*Candida* species cannot be ignored.

Historical reports of IFI in untreated high-risk patients range from 15% to 67%.[1–4] The HR cohort in our study had a 16.7% incidence. This rate of IFI is also similar to a report by Reed *et al.* of high-risk patients who received no prophylaxis.[5] The demographics were similar between the high-risk transplants in the Reed study and those reported here with the exceptions that our high-risk patients were more likely to be undergoing retransplantation (77.8% versus 8.05%) and were less likely to return to the operating room (16.7% versus 59.8%). Reed *et al.* were able to reduce the IFI rate in high risk-patients by four-fold using a 5-day prophylaxis regimen of amphotericin B.[7] Another study examining amphotericin B did not show the same rate of decrease in IFI after OLT in high-risk patients. Hadley *et al.* evaluated the safety and efficacy of liposomal amphotericin B 2 mg/kg i.v. daily and fluconazole 400 mg i.v. daily for 14 days in patients undergoing OLT who were at a high risk for IFI.[15] The rates for development of IFI were equivalent between the two agents (18% with L-amB versus 13% with fluconazole) and similar to the present results using weekly fluconazole. The Hadley study did not include an untreated arm and the absolute efficacy of either regimen remains unclear.

The organisms most frequently responsible for an IFI in this study were non-albicans *Candida.* It is possible this may have been the result of our selecting out fungal organisms that were less susceptible to fluconazole owing to the choice and dosing of antifungal for prophylaxis. Of the 30 patients that did not receive weekly fluconazole prophylaxis, only six received non-azole fungal prophylaxis. All six of these patients were considered low risk and none experienced an IFI. Of the other 21 patients in which there was full data, one patient developed an IFI while on fluconazole 200 mg daily and was considered low risk. Given the lack of a placebo control group and the small number of patients receiving non-azole prophylaxis, it is not possible to fully elucidate whether weekly fluconazole decreased rates of IFI, selected out for resistant yeast, or both. The majority of IFIs after OLT occurred within the first 2 months which is consistent with the findings of others.[1,6,15]

Our multivariable analysis of all evaluated OLTs in this study indicated that classification as low risk was the only independent variable that was significantly associated with a reduction in the development of IFI. It may be possible that certain individual risk factors carry less impact on the development of IFI, but this study was not able to analyze that potential.

The limitations of the study are recognized i.e. being single-centred and retrospective in nature; however, these data have several clinical implications. While firm conclusions cannot be made regarding the utility of this strategy for high risk OLTs, we believe our overall incidence of IFIs can be further reduced. The incidence of IFI in this high-risk group was similar to the historically reported rates in high-risk patients receiving more intensive regimens of fluconazole or L-amB.[6,7,15] However, there was no decrease in the rate of IFI in our high-risk cohort compared with a more recent report of untreated high-risk patients.[5] While further studies are required to determine the optimal prophylaxis strategy for decreasing the rate of IFI in high-risk OLTs, the present findings support the use of the 2009 IDSA invasive candidiasis guidelines for defining patients at high risk for developing IFI after OLT and the recommended prophylaxis strategy set forth by this group may lead to a reduction in our IFI rate in this population. The findings of fluconazole-resistant fungi, coupled with the low rates of IFI in patients deemed low risk for IFIs, suggests that the use of weekly fluconazole for the prevention of oral candidiasis in low-risk patients may not be warranted.

Conflicts of interest

None declared.

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